

WHAT IS CLAIMED IS:

1. A glycopeptide of the formula $A_1\text{---}A_2\text{---}A_3\text{---}A_4\text{---}A_5\text{---}A_6\text{---}A_7$, in which each dash represents a covalent bond; wherein the group A_1 comprises a modified or unmodified α -amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl; where each of the groups A_2 to A_7 comprises a modified or unmodified α -amino acid residue, whereby (i) the group A_1 is linked to an amino group on the group A_2 , (ii) each of the groups A_2 , A_4 and A_6 bears an aromatic side chain, which aromatic side chains are cross-linked together by two or more covalent bonds, and (iii) the group A_7 bears a terminal carboxyl, ester, amide, or N-substituted amide group;
- and wherein one or more of the groups A_1 to A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues; wherein at least one of said sugar residues is a disaccharide modified to bear one or more substituents of the formula YXR , $N^+(R_1)=CR_2R_3$, $N=PR_1R_2R_3$, $N^+R_1 R_2R_3$ or $P^+R_1R_2R_3$ in which the group Y is a single bond, O, NR₁ or S; the group X is O, NR₁, S, SO₂, C(O)O, C(O)S, C(S)O, C(S)S, C(NR₁)O, C(O)NR₁, or halo (in which case Y and R are absent); and R, R₁, R₂, and R₃ are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof; provided that at least one of the substituents of the formula YXR is not hydroxyl; X and Y are not both O; X and Y are not S and O, or O and S,

respectively; and if two or more of said substituents are present, they can be the same or different; and

- provided that when A₄ is linked to a disaccharide having a glucose residue that bears an N-substituted aminohexose residue, then said glucose residue is modified to bear
- 5 at least one of said substituents YXR, N⁺(R₁)=CR₂R₃, N=PR₁R₂R₃, N⁺R₁R₂R₃ or P⁺
R₁R₂R₃.
2. The glycopeptide of claim 1 in which said disaccharide comprises two hexose residues linked to A₄ and wherein at least the hexose residue linked directly to A₄ is modified to bear at least one of said substituents YXR, N⁺(R₁)=CR₂R₃, N=PR₁R₂R₃,
- 10 N⁺R₁R₂R₃ or P⁺R₁R₂R₃.
3. The glycopeptide of claim 2 in which said substituent is attached to the C6 position of said hexose residue linked directly to A₄.
4. The glycopeptide of claim 3 in which said hexose residue linked directly to A₄ is glucose.
- 15 5. The glycopeptide of claim 4 in which at least one of said substituents is YXR wherein Y is a single bond and X is O, NR₁, S or SO₂.
6. The glycopeptide of claim 5 wherein X is NR₁.
7. The glycopeptide of claim 5 wherein X is S.
8. The glycopeptide of claim 5 wherein X is SO₂.
- 20 9. The glycopeptide of claim 5 wherein X is O and R is not H.
10. The glycopeptide of claim 4 wherein at least one of said substituents YXR is halogen.

11. The glycopeptide of claim 2 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
12. The glycopeptide of claim 3 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
- 5 13. The glycopeptide of claim 4 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
14. The glycopeptide of claim 5 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
15. The glycopeptide of claim 6 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a 10 dalbaheptide.
16. The glycopeptide of claim 7 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
17. The glycopeptide of claim 8 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
- 15 18. The glycopeptide of claim 9 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
19. The glycopeptide of claim 10 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
20. The glycopeptide of claim 11, wherein A₆ in said dalbaheptide is linked via a glycosidic bond to one or more sugar residues.
21. The glycopeptide of claim 11 wherein the amino acids in said dalbaheptide are those in vancomycin.

22. The glycopeptide of claim 20 wherein A₁, which is N-methyl leucine, has been selectively removed and replaced with another of said groups A₁.
23. The glycopeptide of claim 2 in which the other hexose residue bears at least one of said substituents.
- 5 24. The glycopeptide of claim 3 in which the other hexose residue bears at least one of said substituents.
25. The glycopeptide of claim 4 in which the other hexose residue bears at least one of said substituents.
- 10 26. The glycopeptide of claim 5 in which the other hexose residue bears at least one of said substituents.
27. The glycopeptide of claim 6 in which the other hexose residue bears at least one of said substituents.
28. The glycopeptide of claim 7 in which the other hexose residue bears at least one of said substituents.
- 15 29. The glycopeptide of claim 8 in which the other hexose residue bears at least one of said substituents.
30. The glycopeptide of claim 9 in which the other hexose residue bears at least one of said substituents.
31. The glycopeptide of claim 10 in which the other hexose residue bears at 20 least one of said substituents.
32. The glycopeptide of claim 11 in which the other hexose residue bears at least one of said substituents.

33. The glycopeptide of claim 12 in which the other hexose residue bears at least one of said substituents.
34. The glycopeptide of claims 13 in which the other hexose residue bears at least one of said substituents.
- 5 35. The glycopeptide of claims 14 in which the other hexose residue bears at least one of said substituents.
36. The glycopeptide of claim 23 wherein at least one of said substituents is YXR wherein Y is a single bond and X is O, NR₁, S or SO₂.
37. The glycopeptide of claim 36 wherein X is NR₁.
- 10 38. The glycopeptide of claim 37 wherein said substituent is attached to C3 of said other hexose residue.
39. A chemical library comprising a plurality of glycopeptides, each of said glycopeptides having the formula A₁-A₂-A₃-A₄-A₅-A₆-A₇, in which each dash represents a covalent bond; wherein the group A₁ comprises a modified or unmodified α-amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl; where each of the groups A₂ to A₇ comprises a modified or unmodified α-amino acid residue, whereby (i) the group A₁ is linked to an amino group on the group A₂, (ii) each of the groups A₂, A₄ and A₆ bears an aromatic side chain, which aromatic side chains are cross-linked together by two or more covalent bonds, and (iii) the group A₇ bears a terminal carboxyl, ester, amide, or N-substituted amide group;

- and wherein one or more of the groups A₁ to A₇ is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues; wherein at least one of said sugar residues is a disaccharide modified to bear one or more substituents of the formula YXR, N⁺(R₁)=CR₂R₃, N=PR₁R₂R₃, N⁺R₁R₂R₃ or P⁺R₁R₂R₃ in which
- 5 the group Y is a single bond, O, NR₁ or S; the group X is O, NR₁, S, SO₂, C(O)O, C(O)S, C(S)O, C(S)S, C(NR₁)O, C(O)NR₁, or halo (in which case Y and R are absent); and R, R₁, R₂, and R₃ are independently hydrogen, alkyl, aryl, aralkyl; alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof; provided that at least one of the substituents of the formula YXR is not hydroxyl; X and Y are not both O; X and Y are not S and O, or O and S, respectively; and if two or more of said substituents are present, they can be the same or different; and
- provided that when A₄ is linked to a disaccharide having a glucose residue that
- 15 bears an N-substituted aminohexose residue, then said glucose residue is modified to bear at least one of said substituents YXR, N⁺(R₁)=CR₂R₃, N=PR₁R₂R₃, N⁺R₁R₂R₃ or P⁺R₁R₂R₃.
40. The chemical library of claim 39 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide and wherein said disaccharide comprises two hexose residues linked to A₄
- 20 and wherein at least the hexose residue linked directly to A₄ is modified to bear said substituent at the C6 position.

41. The chemical library of claim 40 wherein the other hexose residue bears a group YXR in which Y is a single bond and X is NR₁.

42. A method for preparing a glycopeptide comprising the steps of:

(a) selecting a protected glycopeptide of the formula A₁-A₂-A-₃-A₄-A₅-A₆-

5 A₇, in which each dash represents a covalent bond; wherein the group A₁ comprises a modified or unmodified α -amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl; where each of the groups A₂ to A₇ comprises a modified or unmodified α -amino acid residue, whereby (i) the group A₁ is linked to an amino group on the group A₂, (ii) each of the groups A₂, A₄ and A₆ bears an aromatic side chain, which aromatic side chains are cross-linked together by two or more covalent bonds, and (iii) the group A₇ bears a terminal carboxyl, ester, amide, or N-substituted amide group;

at least A₄ is linked to a glycosidic group which has a hexose residue

10 A₁₅ linked to A₄; and said protected glycopeptide has no free amino or carboxyl groups and has a free primary hydroxyl group only at the 6-position of said hexose residue;

(b) contacting said protected glycopeptide with a compound ArSO₂G in

which Ar is an aryl group and G is a leaving group under conditions effective to allow reaction of said free primary hydroxyl group to form a glycopeptide sulfonate ester;

15 (c) contacting said glycopeptide sulfonate ester with a nucleophile under conditions effective to allow displacement of a sulfonate group to produce a substituted glycopeptide.

43. The method of claim 42 in which said nucleophile is a thiol compound.
44. The method of claim 42 in which said nucleophile is a halide.
45. The method of claim 44 in which said halide-substituted glycopeptide is contacted with a second nucleophile under conditions effective to allow displacement of
5 said halide to produce a second substituted glycopeptide.
46. The method of claim 45 in which said second nucleophile is a thiol compound.
47. The method of claim 42 in which the nucleophile is an azide ion, and further comprising reduction of an azido group at the 6-position of the substituted
10 glycopeptide to an amino group.
48. The method of claim 47 further comprising the step of introducing a substituent onto said amino group.
49. The method of claim 42 in which the nucleophile is an azide ion, and further comprising a step of contacting said substituted glycopeptide with a phosphine
15 compound under conditions effective to allow formation of an iminophosphorane.
50. A method for producing the chemical library of claim 39, said method comprising at least two steps in each of which a substituent is introduced on a glycopeptide.
51. The method of claim 50 wherein at least one of said two steps comprises
20 introducing a substituent on the 6-position of a hexose residue directly linked to A₄.
52. The method of claim 51 wherein the other of said at least two steps comprises introducing an N-substituent on an aminohexose residue bonded to said hexose residue directly linked to A₄.

53. The method of claim 52 wherein said hexose residue directly linked to A₄ is a glucose residue.
54. The method of claim 51 wherein A₁-A₂-A₃-A₄-A₅-A₆-A₇ form a dalbaheptide.
- 5 55. The method of claim 54 wherein the amino acids in said dalbaheptide are those in vancomycin.
56. The method of claim 55 wherein A₁, which is N-methyl leucine, has been selectively removed and replaced with another of said groups A₁.
57. A method of preparing a glycopeptide comprising:
- 10 (a) selecting: (i) an aglycone that is soluble in one or more organic solvents, is derived from a glycopeptide antibiotic, and which aglycone has exactly one free phenolic hydroxyl group; and (ii) a protected first glycosyl donor;
- (b) allowing a first non-enzymatic glycosylation reaction to proceed in an organic solvent such that a first glycosidic bond is formed, which links said free phenolic hydroxyl group to the anomeric carbon of the first glycosyl donor to provide a pseudoaglycone having a protected first glycosyl residue;
- 15 (c) selectively removing one protecting group from the first glycosyl residue to provide a pseudoaglycone bearing exactly one free hydroxyl group on the first glycosyl residue;
- (d) selecting a second protected glycosyl donor; and
- (e) allowing a second non-enzymatic glycosylation reaction to proceed in an organic solvent such that a second glycosidic bond is formed, which links said free

hydroxyl group on the pseudoaglycone to the anomeric carbon of the second glycosyl donor.

58. A method of preparing a glycopeptide comprising:

5 (a) selecting a protected glycopeptide antibiotic that is soluble in one or more organic solvents,

(b) contacting the glycopeptide antibiotic with a Lewis acid, and allowing a degradation reaction to proceed such that a sugar residue is removed, producing a pseudoaglycone having exactly one free hydroxyl group on a sugar residue of the pseudoaglycone;

10 (c) selecting a protected glycosyl donor; and

(d) allowing a non-enzymatic glycosylation reaction to proceed in an organic solvent such that a glycosidic bond is formed which links the free hydroxyl group on the pseudoaglycone to the anomeric carbon of the glycosyl donor.

59. The method of claim 57 in which each of the first glycoside and the 15 second glycosyl donor is a monosaccharide bearing an activated anomeric sulfoxide group.

60. The method of claim 58 in which the glycosyl donor is a monosaccharide bearing an activated anomeric sulfoxide group.

61. The method of claim 59 in which BF_3 is present in the first non-enzymatic 20 glycosylation reaction.

62. The method of claim 61 in which the first glycosyl donor is a glucose.

63. The method of claim 60 in which the glycopeptide antibiotic is vancomycin.

64. The method of claim 60 in which the glycopeptide antibiotic is vancomycin.
65. The method of claim 63 in which the Lewis acid is boron trifluoride.
66. The method of claim 63 in which the glycopeptide antibiotic is rendered soluble in organic solvents by substitution with protecting groups.
- 5 67. The method of claim 66, further comprising removal of said protecting groups subsequent to step (d).
68. The method of claim 67 in which said protecting groups comprise: aloc groups substituted on amine nitrogens, an allyl ester group, allyl phenolic ether groups, and acetates of aliphatic hydroxyls.
- 10 69. The method of claim 57 in which the aglycone is rendered soluble in organic solvents by substitution with protecting groups.
70. The method of claim 69, further comprising removal of said protecting groups and protecting groups on the glycosides following step (e).
- 15 71. The method of claim 70 in which said protecting groups comprise: a CBz group on the amine nitrogen, a benzyl ester group, methyl phenolic ether groups on residues 5 and 7, and acetates of aliphatic hydroxyls.
72. The method of claim 57 in which the glycopeptide is attached to a polymeric support.
- 20 73. The method of claim 58 in which the glycopeptide is attached to a polymeric support.

74. A method for producing the chemical library of claim 39; said method comprising at least two steps, wherein at least one of said at least two steps comprises a glycosylation reaction which introduces a substituted sugar residue.

75. The method of claim 74 in which A₁ to A₇ are linked sequentially by 5 peptide bonds and cross-linked as in a dalbaheptide.

76. The method of claim 75 in which said glycosylation reaction links said substituted sugar residue to an A₄ residue of an aglycone.

77. The method of claim 76 in which said glycosylation reaction links said substituted sugar residue to a sugar residue of a pseudoaglycone, wherein said sugar 10 residue of a pseudoaglycone is linked to an A₄ residue of the pseudoaglycone.

78. The method of claim 76 in which a second glycosylation reaction links a second substituted sugar residue to said substituted sugar residue.

79. The method of claim 77 in which A₁ is a modified or unmodified α-amino acid residue, and in which A₁ to A₇ are linked sequentially by peptide bonds and 15 cross-linked so as to have the structure of a dalbaheptide.

80. The method of claim 78 in which A₁ is a modified or unmodified α-amino acid residue, and in which A₁ to A₇ are linked sequentially by peptide bonds and cross-linked so as to have the structure of a dalbaheptide.

81. The method of claim 77 in which the structures and interconnections of 20 A₁ to A₇ are those found in vancomycin.

82. The method of claim 81 in which a glycosyl donor bearing an activated anomeric sulfoxide group is employed in each glycosylation reaction.

83. The compound of claim 1 which is
N-4-(4-chlorophenyl)benzylvancosamine-glucose-C6-2-mesitylenesulfonated
vancomycin.
84. The compound of claim 1 which is glucose-C6-2-thio-6-azathymine
5 vancomycin.
85. The compound of claim 1 which is
glucose-C6-2-thio-4-hydroxy-6-methylpyrimidine vancomycin.
86. The compound of claim 1 which is
N-4-(4-chlorophenyl)benzylvancosamine-glucose-C6-2-thio-5-amino-1,3,4-thiadiazole
10 vancomycin.
87. The compound of claim 1 which is
N-4-(4-chlorophenyl)benzylvancosamine-glucose-C6-2-thio-4-amino-3-hydrazineo-1,2,4
-triazole vancomycin.
88. The compound of claim 1 which is
15 N-4-(4-chlorophenyl)benzylvancosamine-glucose-C6-2-thio-4-hydroxy-6-
methylpyrimidine vancomycin.
89. The compound of claim 1 which is
N-4-(4-chlorophenyl)benzylvancosamine-glucose-C6-2-thio-4-hydroxy-6-azathymine
20 vancomycin.
90. The compound of claim 1 which is
N-4-(4-chlorophenyl)benzylvancosamine-glucose-C6-ido vancomycin.
91. The compound of claim 1 which is glucose
-C6-N-2-quinoxalinyln-vancosamine-N-4-(4-chlorophenyl)benzyl vancomycin.

92. The compound of claim 1 which is
vancosamine-N-4-(4-chlorophenyl)benzyl-glucose-C6-S-3-amino-5-mercaptop-1,2,4-triazole vancomycin.
93. The compound of claim 1 which is glucose-C6-mesitylenesulfonyl
5 vancomycin.
94. The compound of claim 1 which is glucose-C6-iodo vancomycin.
95. The compound of claim 1 which is glucose-C6-azide vancomycin.
96. The compound of claim 1 which is glucose-C6-bromo vancomycin.
97. The compound of claim 1 which is glucose-C6-amine vancomycin.
- 10 98. The compound of claim 1 which is glucose-C6-hydrazine vancomycin.
99. The compound of claim 1 which is N-4-(4-chlorophenyl)benzyl
vancosamine-glucose-C6-iminotriphenylphosphorane vancomycin.
100. The compound of claim 1 which is glucose-C6-N-decyl vancomycin.
101. The compound of claim 1 which is N-4-(4-chlorophenyl)benzyl
15 vancosamine-glucose-C6-amine vancomycin.
102. A glycopeptide antibiotic bearing at least one disaccharide group, said disaccharide group comprising two saccharide groups, a first of said saccharide groups bearing at least one amino or substituted amino group, and a second of said saccharide groups modified to bear at least one substituent which is not hydroxyl, or a
20 pharmaceutically acceptable salt thereof.
103. The glycopeptide antibiotic of claim 102 wherein the second of said saccharide groups is glucose modified to bear at least one substituent which is not hydroxyl at the C6 position of said glucose.

104. The glycopeptide antibiotic of claim 103 which is vancomycin modified to bear at least one substituent which is not hydroxyl at the C6 position of said glucose.
105. The glycopeptide antibiotic of claim 104 wherein said at least one substituent which is not hydroxyl at the C6 position of said glucose is amino.
- 5 106. The glycopeptide antibiotic of claim 105 wherein the first of said saccharide groups bears at least one substituted amino group.
107. The glycopeptide antibiotic of claim 106 wherein said substituted amino group is -NR₁H wherein R₁ bears one or more alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic or substituted heterocyclic groups.
- 10 108. The glycopeptide antibiotic of claim 107 wherein at least one of said substituted alkyl groups is aralkyl.
109. The glycopeptide antibiotic of claim 107 wherein at least one of said substituted aryl groups is aralkyloxy substituted aryl.
110. The glycopeptide antibiotic of claim 107 wherein at least one of said substituted aryl groups is halo-substituted aryl.
- 15 111. The glycopeptide antibiotic of claim 102 wherein the first of said saccharide groups bears at least one substituted amino group.
112. The glycopeptide antibiotic of claim 111 wherein said substituted amino group is -NR₁H wherein R₁ bears one or more alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic or substituted heterocyclic groups.
- 20 113. The glycopeptide antibiotic of claim 112 wherein at least one of said substituted alkyl groups is aralkyl.

114. The glycopeptide antibiotic of claim 112 wherein at least one of said substituted aryl groups is aralkyloxy substituted aryl.
115. The glycopeptide antibiotic of claim 112 wherein at least one of said substituted aryl groups is halo-substituted aryl.
- 5 116. The glycopeptide antibiotic of claim 112 wherein said at least one substituent which is not hydroxyl is amino.